IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Confirmation No. 8747
Applicant: Norihito SHIMONO et al.
Appln. No.: 10/048,063 Group Art Unit: 1615
Filed: January 28, 2002 Examiner: Micah Paul YOUNG
For: SOLID PREPARATION CONTAINING CHITOSAN POWDER AND PROCESS FOR PRODUCING THE SAME

SUPPLEMENTAL DECLARATION

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

I, Norihito SHIMONO, a citizen of Japan and residing at No. 3-13, Ibukidainishi-machi 6-chome, Nishi-ku, Kobe-shi, Hyogo, Japan, declare and say as follows.

1. In my former Declaration executed on 25th day of July, 2006, the preparations of the present invention were compared with the preparations of Examples 3, 4, 5, 7 and 8 of the cited Lerner et al. USPN 5,840,332 (wherein the ratio of the dispersed particles (a) : the water-insoluble polymer (b) being 7 : 3) with respect to (1) release of active ingredient with 1st fluid (artificial gastric juice) (Experiment 1), and (2) release of active ingredient with changing the dissolution media: 1st fluid (pH 1.2) - 2nd fluid (pH 6.8) - an acidic aqueous solution (pH 4.0) (Experiment 2) in order to prove the superior (sustained) release properties of the preparations of the present invention.

It was further tested in my former Declaration the effects of the ratio of the dispersed particles (a): the water-insoluble polymer (b) in the preparations of the present invention with respect to release of active ingredient (Experiment 3) and thereby it was proved that the preparations of the present invention showed excellent release properties within the claimed ratio of (a) and (b), i.e. 4:1 to 1:4, and it was further tested the effects of the enteric coating in the preparations of the present invention with respect to

release of active ingredient with changing the dissolution media: 1st fluid (pH 1.2) - 2nd fluid (pH 6.8) - an acidic aqueous solution (pH 4.0) (Experiment 4) and also *in vivo* test of release of active ingredient in rats (Experiment 5) and thereby it was proved that the preparations of the present invention showed excellent active ingredient-release properties.

2. In addition to comparative experiments in my former Declaration, the following tests have been done under my direction for comparison of the preparations of the present invention with the preparations of the cited Lerner et al. USPN 5,840,332 having other ratios of the dispersed particles (a) : the water-insoluble polymer (b) such as 1 : 1 and 3 : 7 as shown in Examples 3, 7 and 8 of said Lerner et al., and further for studying the effects of the ratio of the dispersed particles (a) : the water-insoluble polymer (b) and also the particle size of chitosan, and further effects of the kind of the water-insoluble polymer on the active ingredient-release properties.

(1) Test preparations

The following preparations were subjected to the experiments.

(1)-1. Preparation of Ref. prepar. A(1/1), A(3/7), D(1/1), D(3/7), E(1/1), E(3/7) of Lerner et al. USPN 5,840,332:

Ref. prepar. A(1/1), A(3/7), D(1/1), D(3/7), E(1/1), and E(3/7) were prepared along with the formulations disclosed in Examples 3, 7 and 8 of Lerner et al. excepting that the core tablets containing 30 mg sodium salicylate (active ingredient) (each tablet; weighing 300 mg, diameter 10 mm) by standard direct tableting method using microcrystalline cellulose and calcium pectinate. The core tablets thus obtained were coated with a coating suspension of dispersed particles (e.g. calcium pectinate)/ water-insoluble polymer (e.g. Eudragit E) as shown in Table 1A by a conventional film coating method.

(1)-2. Preparation of Prepar. F, G, H, I, J, M, N, and O of the present invention:

Prepar. F, G, H, I, and J of the present invention were prepared in the same manner as described in my former Declaration executed on 25th day of July, 2006. Besides, Prepar. M, N, and O of the present invention were prepared likewise, while in Prepar. M, the chitosan powder to be dispersed in the water-insoluble polymer was the pulverized one (particle size, 6 μm) like in Prepar. F, G, H, I and J, and the chitosan powder in Prepar. N was the unpulverized one (particle size, 110 μm), and further, the water-insoluble polymer was ethyl cellulose in Prepar. M and N and it was Eudragit NE30D®

in Prepar. O. The coating was carried out by a conventional film coating method like in the above (1)-1 for Ref. preparations excepting using the coating compositions shown in Table 1A.

Table 1A

Test Preparation	a: Dispersed particles	b: Water-insoluble polymer	a:b
Ref. prepar. A(1/1) (=Ex.3 of Lerner et al.)	Calcium pectinate	Eudragit E®	1:1
Ref. prepar. A(3/7) (=Ex.3 of Lerner et al.)			3:7
Ref. prepar. D(1/1) (=Ex.7 of Lerner et al.)	Crospovidone		1:1
Ref. prepar. D(3/7) (=Ex.7 of Lerner et al.)			3:7
Ref. prepar. E(1/1) (=Ex.8 of Lerner et al.)	Microcrystalline cellulose		1:1
Ref. prepar. E(3/7) (=Ex.8 of Lerner et al.)			3:7
Prepar. F (The present invention)	Chitosan	Eudragit RS®	4:1
Prepar. G (The present invention)			2:1
Prepar. H (The present invention)			1:1
Prepar. I (The present invention)			1:2
Prepar. J (The present invention)			1:4
Prepar. M (The present invention)	Chitosan	Ethyl cellulose	2:1
Prepar. N (The present invention)	Chitosan (unpulverized)		2:1
Prepar. O (The present invention)	Chitosan	Eudragit NE30D®	2:1

(2) Experiments

(2)-1. Experiment 1A:

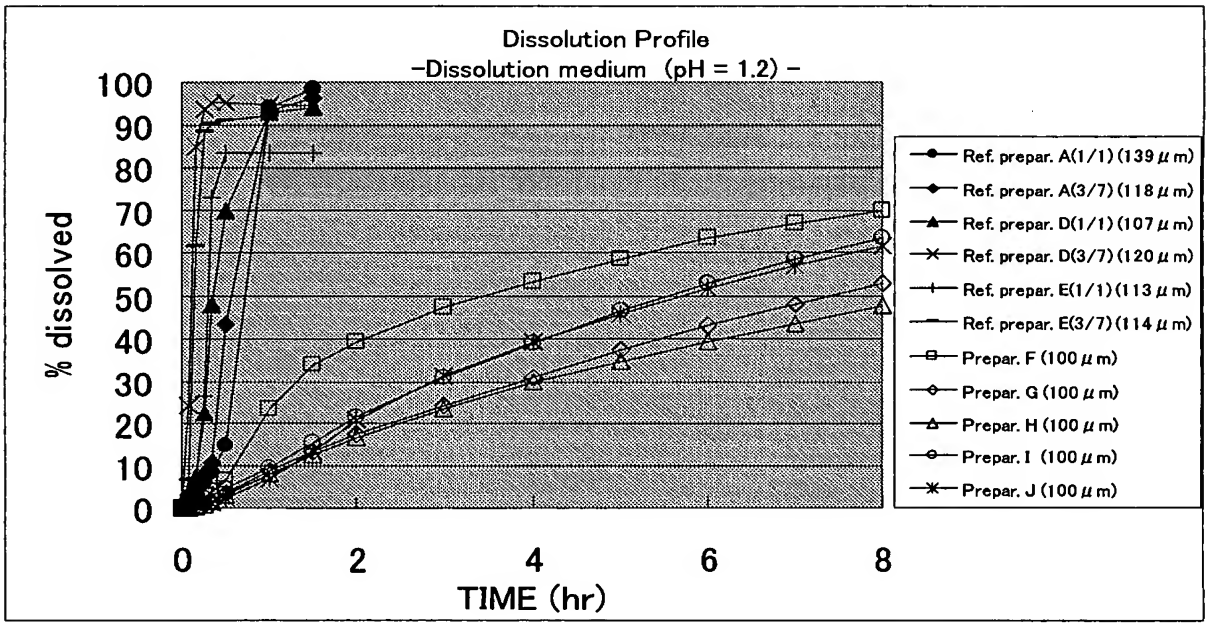
Comparison of release of active ingredient with 1st fluid (artificial gastric juice) between Ref. prepar. A(1/1), A(3/7), D(1/1), D(3/7), E(1/1),E(3/7) of Lerner et al. which had the ratio of (a):(b) = 1:1 or 3:7 and Prepar. F, G, H, I, and J of the present invention which had the ratio of (a):(b) within the claimed ratios of 1:4 to 4:1

The dissolution profile (release of the active ingredient) was tested with respect to the tablet preparations of Lerner et al. and the preparations of the present invention by Paddle method as defined in Japanese Pharmacopeia using 1st fluid (pH 1.2, 900 ml) at 50 rpm, 37°C.

The results are shown in the following Fig. 1A. In Fig. 1A, the

thickness of the coating layer of the preparations is shown in the parenthesis after each preparation. For instance, Ref. prepar. A(1/1) (139 μm) means that the Ref. prepar. A(1/1) has a thickness of coating layer of 139 μm. It is the same in all preparations in Fig. 1A to Fig. 3A hereinafter.

Fig. 1A



As is seen from the above results shown in Fig. 1A, even when the ratio of (a):(b) was changed to 1:1 or 3:7, the preparations of Lerner et al. showed very rapid dissolution profile as like as the reference preparations A, B, C, D having the ratio of (a):(b) of 7:3 tested in my former Declaration (see Fig. 1). As I assumed in my former Declaration, in the Ref. preparations, the tablets would be swollen with the 1st fluid and then disintegrated, by which the active ingredient was dissolved out very rapidly.

On the other hand, in Prepar. F, G, H, I and J of the present invention with the claimed ratio of (a):(b) of 1:4 to 4:1, the coating of the tablets would not be swollen and the original tablet form was kept for more than 8 hours, and thereby the active ingredient was dissolved out very gradually.

It shall also be noted that although Ref. Prepar. A(1/1), A(3/7), D(1/1), D(3/7), E(1/1),E(3/7) of Lerner et al. had a larger coating thickness of from 139 to 107 μm than that (100 μm) of the preparations of the present invention, the Ref. preparations of Lerner et al. dissolved more rapidly.

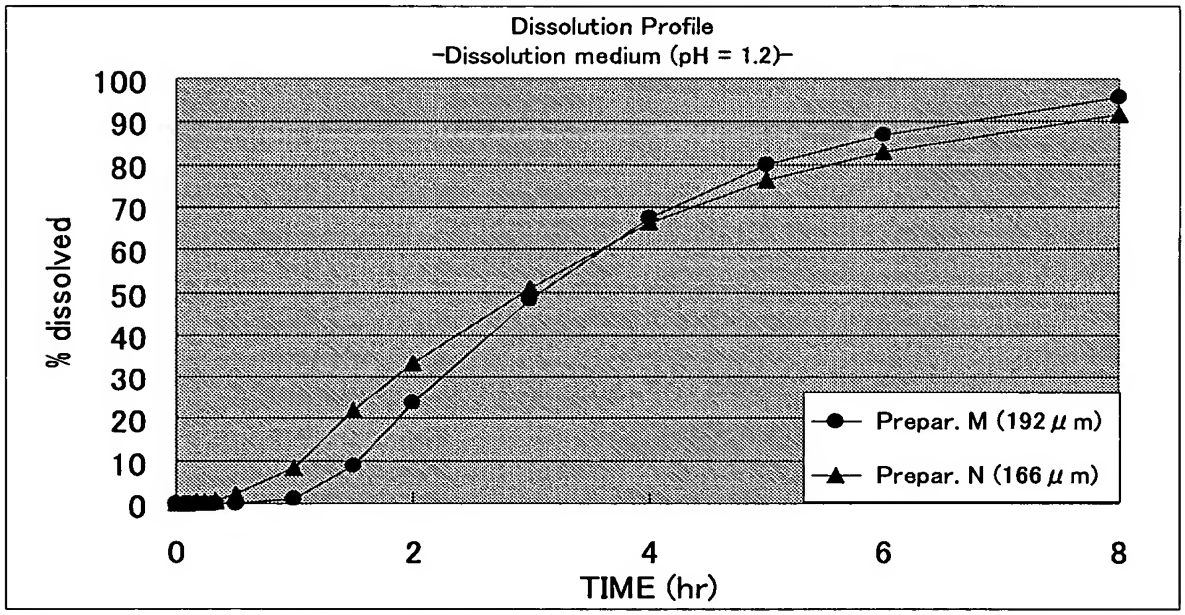
This suggests that the dissolution profile of the preparations was almost not effected by thickness of the coating layer, but was effected much more by the kinds of the dispersed particles in the coating layer.

Thus, the preparations of the present invention having a ratio of (a):(b) of 1:4 to 4:1 showed superior release profile (sustained release properties) in comparison with the preparations of Lerner et al, though the former had a smaller coating thickness than the latter.

(2)-2. Experiment 2A

With respect to Prepar. M and Prepar. N of the present invention using ethyl cellulose as the water-insoluble polymer, the dissolution profile was tested in the same manner as in the above Experiment 1A, and the results are shown in the following Fig. 2A.

Fig. 2A



As is seen from the above results shown in Fig. 2A, the Prepar. M and N of the present invention using ethyl cellulose as the water-insoluble polymer showed excellent sustained release properties as like as the Prepar. F, G, H, I and J of the present invention using other water-insoluble polymer, Eudragit RS (see the above Fig. 1A as well as Fig. I in my former Declaration).

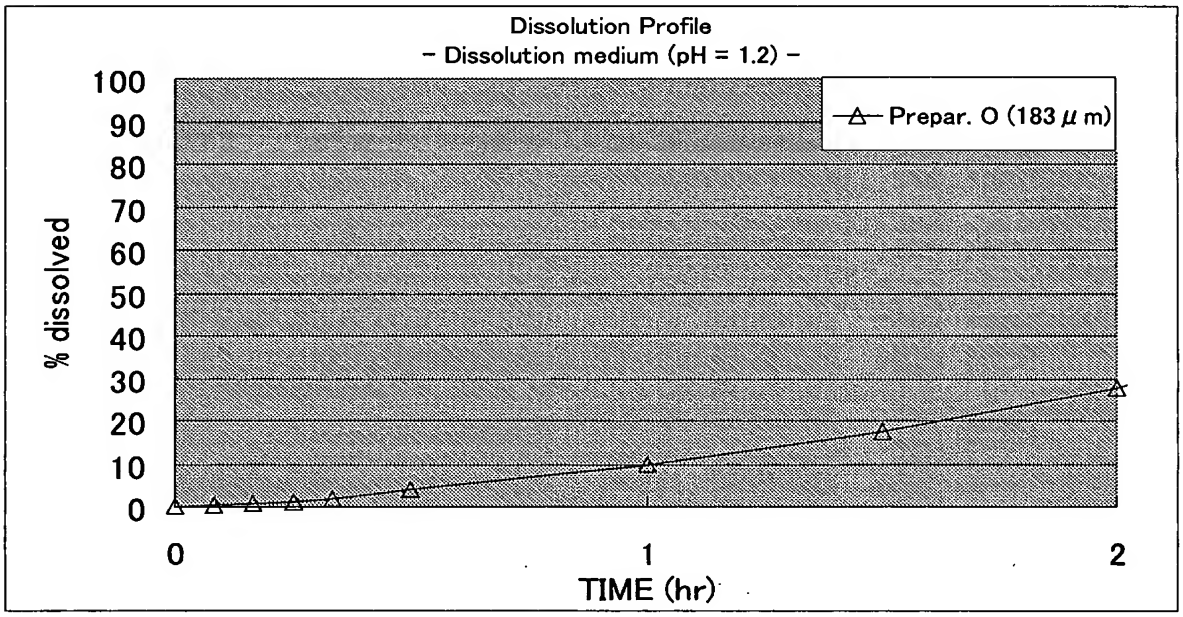
Furthermore, although in these Prepar. M and N, the chitosan powder to be dispersed in the water-insoluble polymer had a different particle size, that is, chitosan powder in Prepar. M was the pulverized one

(particle size, 6 μm) and the chitosan powder in Prepar. N was the unpulverized one (particle size, 110 μm), the excellent release profiles were similar to each other.

(2)-3. Experiment 3A

With respect to Prepar. O of the present invention using Eudragit NE30D® as the water-insoluble polymer, the dissolution profile was tested in the same manner as in the above Experiment 1A, and the results are shown in the following Fig. 3A.

Fig. 3A



As is seen from the above results shown in Fig. 3A, the Prepar. O of the present invention showed excellent sustained release properties as like as the Prepar. F, G, H, I and J of the present invention using other water-insoluble polymer, Eudragit RS (see the above Fig. 1A as well as Fig. 1 to Fig. 3 in my former Declaration).

3. It is my opinion based upon my knowledge and experience in this field that

in the reference preparations disclosed in the cited Lerner et al. reference, even when the ratio of the dispersed particles (a) and the water-insoluble polymer (b) of the coating film was varied to 1:1 and 3:7, the reference preparations of Lerner et al. released the active ingredient very rapidly by the treatment with 1st fluid (artificial gastric juice) as like

as the reference preparations having the ratio of (a):(b) of 7:3 as shown in my former Declaration, and further even when the thickness of the coating film on the core was made larger (e.g. 193 - 107 μm) than that (100 μm) of the preparations of the present invention, the dissolution properties were not changed, which means that according to the preparations of the cited Lerner et al., it is difficult to control the rapid release of the active ingredient in the stomach and hence is not suitable for sustained release preparation;

on the other hand, the preparations of the present invention using chitosan as the dispersed particles in the coating layer could give the desired sustained release of the active ingredient from the stomach to the large intestine with keeping the original shapes of tablets/pellets without swelling or disintegration, even though the ratio of the dispersed particles (a) and the water-insoluble polymer (b) of the coating film was varied, and further the kind of the water-insoluble polymer was changed to ethyl cellulose or Eudragit NE30D® from Eudragit RS® used in Prapar. F, G, H, I and J, the excellent sustained release properties were not affected,

as seen from Experiments 2 and 4 in my former Declaration, the preparations of the present invention in various embodiments as defined in claims could show continuous release of the active ingredient by the treatment with 1st fluid (pH 1.2, for 2 hours), 2nd fluid (pH 6.8, for 3 hours) and the weak acidic aqueous solution (pH 4.0, for 3 hours) which are simulated to the conditions (pH value and time of passing through) in the digestive tract in biobody; and further the enteric coating colonic delivery preparation of the present invention can keep the original shape of preparation (tablets and pellets) even by treating with 1st fluid (pH 1.2, for 2 hours) and 2nd fluid (pH 6.8, for 3 hours), that is, for about 5 hours after administration and until reaching to around the large intestine, and when reached to around the large intestine (after about 4-5 hours), the blood concentration of the active ingredient increases, and hence, such an enteric coating preparation of the present invention is suitable as a colonic delivery preparation, which would never been predicted from the disclosure of the cited Lerner et al. reference;

as is seen from Experiment 1A (Fig. 1A), although Ref. prepar. A(1/1), A(3/7), D(1/1), D(3/7), E(1/1), E(3/7) of Lerner et al. had a larger coating thickness of from 139 to 107μm than that (100 μm) of the preparations of the present invention, the Ref. preparations of Lerner et al. dissolved more rapidly, which suggests that the dissolution profile of the preparations was almost not affected by thickness of the coating layer, but

was affected much more by the kinds of the dispersed particles in the coating layer; and further as is seen from Experiment 2A (Fig. 2A), although the preparations had different particle size of chitosan, that is, the pulverized one (particle size, 6 μm) in Prepar. M and the unpulverized one (particle size, 110 μm) in Prepar. N, and further had different thickness of the coating, i.e. 192 μm (Prepar. M) and 166 μm (Prepar. N), the excellent release profiles were similar to each other, which proved that the excellent sustained release properties of the preparations of the present invention are not substantially affected by the chitosan particle size or by the thickness of the coating; and

Lerner et al. mention as "Drug release is controlled by varying the following parameters; (1) size of the particulate matter; (2) thickness of the coating; (3) type of material forming the particulate matter; (4) ratio of particulate matter; and (5) water-insoluble film forming material." (cf. Lerner et al. USPN 5,840,332, Col. 11, lines 51-55), but it has been found that among the above parameters the item (3) type of material forming the particulate matter was the most important while other parameters such as (1) size of the particulate matter (the dispersed particle), (2) thickness of the coating film, (4) the ratio of the particulate matter, and (5) the kinds of the water-insoluble polymer were not so important parameters, and it would have never been predicted from the cited Lerner et al. reference that the preparations of the present invention using chitosan as the dispersed particles (the particulate matter in Lerner et al.) give such excellent sustained release properties.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

This 12th day of April, 2007

Norihito Shimono

Norihito Shimono